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Original Article

Increased plasma anti-cardiolipin antibodies are associated with acute ischemic stroke

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Abstract: Objective: It has been shown that patients with cerebral infarction are more likely to test positive for plasma anti-cardiolipin antibodies (ACA). However, the function of ACA in acute ischemic stroke (AIS) remains unclear. This study aimed to assess the clinical implications of plasma ACA in patients with acute ischemic stroke. Methods: One hundred fifty-three patients who had a first ischemic stroke were enrolled in the study. The presence of plasma ACA was determined by ELISA, and the National Institutes of Health Stroke Scale score was used to assess the severity of the patients' condition at admission. The Barthel index was employed to determine 3-month functional outcomes. Results: The rate of positive plasma ACA was higher among AIS cases compared with controls. ACA were an independent diagnostic biomarker for AIS. Patients with smaller cerebral infarctions had a higher rate of positive plasma ACA compared to those with larger cerebral infarctions, and those with mild stroke had a higher rate than those with severe stroke. Furthermore, the rate of positive plasma ACA was higher in AIS patients with worse outcomes than in those with better outcomes ($P<0.001$). Regression analysis showed that ACA was also an independent predictor of functional outcomes. Conclusion: Lower rates of positive plasma ACA are associated with greater stroke severity and a larger infarction volume among AIS patients. Therefore, ACA can be used as an independent diagnostic and predictive biomarker of AIS.

Keywords: Anti-cardiolipin antibodies, acute ischemic stroke, plasma, marker

Introduction

Stroke is the most common cerebrovascular disease and can lead to disability and death [1, 2]. Ischemic stroke accounts for 80-85% of all strokes; the remainder are hemorrhagic [3]. Stroke imposes a significant burden on human health [4]. Ischemic stroke is caused by an interruption of cerebral blood flow due to a blood clot [5, 6]. Early control of risk factors and evaluation of the disease's prognosis and severity are important for effective treatment that aims to improve the functional outcome.

There is large body of evidence supporting the viewpoint that inflammation is crucial in the pathophysiologic processes of acute ischemic stroke (AIS) [7]. During AIS, inflammatory responses occur in both the peripheral and central nervous systems (CNS) [8]. After the onset of ischemic stroke, the inflammatory cascade results in damage to the blood-brain barrier, which then allows activated peripheral immune cells, such as neutrophils and T-cells, to penetrate and accumulate in the ischemic brain region [9]. Many recent studies have suggested that while inflammation may increase tissue injury, it may also be beneficial to the reparative process [8, 10]. After cerebral ischemia, inflammatory responses both within and outside the brain promote brain inflammation by producing inflammatory mediators such as cytokines, which promote the scavenging of necrotic debris after AIS [11]. There is a growing body of evidence to show that decreased levels of pro-inflammatory cytokines and increased levels of anti-inflammatory cytokines are correlated with a smaller infarct size and a better clinical outcome, suggesting that the balance between pro- and anti-inflammatory cytokines determines the susceptibility to AIS and its prognosis [12]. Thus, biomarkers of pro- or anti-inflammatory cytokines could provide an early diagnostic and prognostic indicator of ischemic stroke. However, no suitable biomarker has yet been identified.

Anti-cardiolipin antibodies (ACA) can affect phospholipid-binding proteins, which influence the prothrombin activator complex [13, 14]. The role of phospholipids in the pathophysiology of cardiovascular and venous thrombotic events is well known [15]. It has been shown that a positive plasma ACA test is more common among young patients who have coronary artery disease, in whom it is considered to be a risk factor [16]. A higher incidence of positive ACA is also seen in patients with acute myocardial infarction [16]. Several studies have found that ACA are widely expressed in the brain and spinal cord, suggesting that they may have specific functions in the central nervous system [17]. Recently, studies also reported that ACA have been implicated in certain CNS diseases, such as Alzheimer's disease and experimental autoimmune encephalomyelitis [18]. Thus, ACA may have a role in the progression of AIS.

To date, there is no available study of the relationship between ACA and the functional outcome in AIS patients. Therefore, the purpose of this study was to determine whether plasma ACA can be used as a possible prognostic and diagnostic marker in these patients.

Materials and methods

Patients and clinical characteristics

One hundred fifty-three first-ever AIS patients were recruited at Tianjin Baodi Hospital. All patients were diagnosed as having AIS according to the criteria of the World Health Organization, based on symptoms during the previous 72 hours. One hundred age- and sex-matched healthy individuals were selected and constituted the healthy control group. Patients with the following conditions were excluded: heart failure, history of trauma, surgery or trauma within the last 2 months, renal dysfunction, liver insufficiency, serious infections, and Th2-related diseases such as asthma, atopic dermatitis, and anaphylaxis. The protocol was approved by the ethics committee of Tianjin Baodi Hospital. All subjects or their relatives were informed about the research and consent forms were signed before enrolment.

Collection of the related data

We retrieved the following baseline clinical information: sex, age, risk factors (hyperlipidemia, diabetes mellitus, alcohol abuse, smoking habit, hypertension, and atrial fibrillation) and several biochemical indices. All participants were examined using magnetic resonance imaging (MRI) or computed tomography (CT) scans. The infarct area was calculated using the formula: $0.5 \times a \times b \times c$ where a represents the greatest longitudinal diameter of the infarct, b the greatest transverse diameter perpendicular to a, and c the number of 10-mm slices included. A small infarct volume was defined as less than 5 cm^3. The severity of the AIS was determined using the National Institutes of Health Stroke Scale (NIHSS) score on admission. Functional outcomes based on the Barthel index (BI) were evaluated 3 months after admission by evaluators who were blinded to the serum ACA. A BI score below 85 indicated an unfavorable outcome.

Blood sampling and laboratory tests

Blood specimens were collected from all participants at 6:00 in the morning. Specimens were immediately centrifuged and aliquots were stored at a temperature below -80°C for further analysis. Plasma ACA were measured by means of enzyme-linked immunosorbent assays (ELISA). Other parameters, including white blood cell count (WBC), Vitamin D (Vit D), total cholesterol (TC), triglycerides (TG), high-density lipoproteins (HDL), low-density lipoproteins (LDL), and glycated hemoglobin (HbA1c), were also measured using ELISA.

Statistical analysis

Statistical analysis was performed using Prism V software. Results were represented as means for normally distributed variables, medians for non-normally distributed variables, and percentages for categorical variables. Continuous variables were compared between groups using the Mann-Whitney test and proportions were compared using the chi-square test. The relation between serum ACA and functional outcome in AIS was computed using multivariate logistic regression analysis, following adjustment for confounders in the univariate analysis (sex, age, NIHSS score, infarct volume, hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, smoking habit, alcohol abuse, and several biochemical indices). Results were presented as adjusted odds ratio (OR) and corresponding 95% confidence inter-

Table 1. Baseline characteristics of patients with favorable or unfavorable outcomes

Characteristics	Patients	Favorable outcome	Unfavorable outcome	*p* value
	N = 153	n = 109	n = 33	
Age	58 (49-67)	57 (48-66)	59 (49-68)	0.089
Gender M/F	89/64	64/45	19/14	0.34
Systolic blood pressure	161 (144-180)	159 (143-178)	169 (149-189)	0.065
Diastolic blood pressure	84 (77-90)	83 (76-89)	85 (77-88)	0.12
Median NIHSS score	4 (2-6)	3 (1-5)	8 (5-11)	<0.001
Infarction volume	1.34 (0.59-3.34)	1.14 (0.43-2.98)	3.45 (1.34-5.43)	<0.001
Risk factor				
Hypertension	107	75	27	0.087
Diabetes mellitus	34	21	11	0.041
Hypercholesterolemia	41	28	9	0.65
Atrial fibrillation	32	14	3	0.013
Smoking	61	44	8	0.025
Alcohol abuse	42	36	5	<0.001
Laboratory results				
WBC (10^9/L)	6.49 (5.34-7.89)	6.55 (5.45-8.09)	6.32 (5.80-7.72)	0.15
Lithic acid (μmol/L)	280.21 (217.20-365.43)	294.4 (221.80-376.42)	267.5 (209.91-343.12)	0.23
Vit D (nmol/L)	56.18 (37.32-75.32)	59.34 (40.3-78.51)	52.96 (35.34-77.39)	0.25
TC (mmol/L)	4.95 ± 1.03	4.93 ± 1.01	4.97 ± 1.04	0.15
TG (mmol/L)	1.58 (1.18-2.29)	1.60 (1.21-2.43)	1.57 (1.17-2.28)	0.54
HDL (mmol/L)	1.09 (0.95-1.32)	1.07 (0.92-1.3)	1.11 (0.98-1.36)	0.32
LDL (mmol/L)	2.95 ± 0.84	2.92 ± 0.83	2.97 ± 0.86	0.44
Glucose (mmol/L)	4.93 (4.43-6.21)	4.92 (4.42-6.2)	5.19 (4.49-7.98)	0.061
HbA1c	5.83 (5.54-7.23)	5.81 (5.51-7.19)	6.32 (5.82-8.01)	0.018
ACA (%)	40 (26.1)	32 (29.4)	5 (15.2)	<0.001

Data are presented as the median, n (%) or mean (SD). ACA, anti-cardiolipin antibodies; NIHSS, National Institutes of Health Stroke Scale; WBC, Leukocyte; Vit D, Vitamin D; TC, Total cholesterol; TG, Triglycerides; HDL, High-density lipoproteins; LDL, Low-density lipoproteins; HbA1c, Glycated hemoglobin. *p* value was assessed using the Mann-Whitney U test or the Chi-Square test.

Table 2. ACA positive rate in different group

	Stroke patients	Healthy control	*p* value
Case	153	100	
ACA positive	40	3	
%	26.1	3	<0.001

ACA, anti-cardiolipin antibodies.

val (CI). A probability of $P<0.05$ indicated statistical significance.

Results

Baseline characteristics

In the current study, we included 153 cases with AIS, of whom 142 completed 3-month follow-up (11 patients or their relatives refused follow-up). The median NIHSS score at admission was 4 points (2-6). There were unfavorable outcomes in 33 cases (23.23%) (**Table 1**).

ACA and clinical variables

The rate of positive ACA was significantly higher ($P<0.001$) in AIS patients than in healthy controls (**Table 2**). Age, sex, risk factors for stroke, lithic acid, glucose, WBC, TG, TC, HDL, LDL, and HbA1c had no statistical effect on the incidence of ACA in AIS patients ($P>0.05$ for all categories).

In univariate logistic regression analysis, ACA was found to be a predictor of AIS with an unadjusted OR of 1.076 (95% CI, 1.024-1.094; $P = 0.008$). Serum ACA was an independent predictor for AIS with an OR of 1.079 (95% CI, 1.028-1.099; $P<0.001$) after adjusting for all other

Table 3. Univariate logistic regression analysis of ACA

	OR (95% CI)	*p* value
Unadjusted	1.076 (1.024-1.094)	0.008
Adjusted	1.079 (1.028-1.099)	<0.001

ACA, anti-cardiolipin antibodies.

Table 4. Accuracy of serum biomarkers in stroke

Prediction	AUC	95% CI	*p* value
Glucose	0.345	0.261-4.321	<0.001
Lithic acid	0.354	0.271-4.476	<0.001
HbA1c	0.549	0.438-0.672	<0.001
ACA	0.734	0.632-0.801	<0.001

ACA, anti-cardiolipin antibodies; AUC, Area under the curve; CI, Confidence interval; HbA1c, Glycated HDL, High-density lipoproteins; HbA1c, Glycated hemoglobin.

Table 5. Positive rate of serum ACA in different infarction volume and control groups

Group	n	Positive n (%)	*p* value
Small infarct volume	91	28 (30.8)	<0.001[a,b]
Large infarct volume	30	6 (20)	<0.001[c]
Control	100	3 (3)	

a: Comparison of Small infarct volume and Large infarct volume; b: Comparison of Small infarct volume and Control; c: Comparison of Large infarct volume and Control.

Table 6. Positive rate of serum ACA in mild and severe stroke patients and healthy control

Group	n	Positive n (%)	*p* value
Severe stroke group	113	31 (27.4)	<0.001[a,b]
Mild stroke group	40	9 (22.5)	<0.001[c]
Control	100	3 (3)	

a: Comparison of Severe stroke group and Mild stroke group; b: Comparison of Severe stroke group and Control; c: Comparison of Mild stroke group and Control.

significant factors (systolic blood pressure, lithic acid, diastolic blood pressure, WBC, TC, HDL, glucose, and HbA1c) (**Table 3**). In addition, glucose, lithic acid, and HbA1c were independent predictors for AIS. However, compared to glucose, lithic acid, and HbA1c, ACA showed a greater discriminatory ability (**Table 4**).

ACA and cerebral infarction volume

MRI or CT scans were available for 121 patients. We found that patients with a smaller cerebral infarct volume showed a higher rate of positive serum ACA compared to patients with a larger cerebral infarct ($P<0.05$). Moreover, the incidence of a positive ACA test was significantly higher in both these groups than in the control group (**Table 5**).

ACA and severity of AIS

On the basis of the NIHSS scores, the cases were classified into 2 groups: 113 patients with moderate to severe stroke (NIHSS score ≥6) and 40 patients with mild stroke (NIHSS score <6). We found that the rate of positive ACA was lower in the mild stroke group than in the severe stroke group ($P<0.001$). However, the ACA positive rate was higher in both these groups than in the control group ($P<0.001$ for both) (**Table 6**).

ACA and 3-month functional outcomes

Unfavorable outcomes were recorded in 33 cases (23.23%). The plasma ACA positive rate was higher in patients who had favorable outcomes than in those with unfavorable outcomes. Comparing the NIHSS score and other risk factors, as presented in **Table 7**, we found using univariate logistic regression analysis that the rate of positive ACA was associated with a favorable outcome (unadjusted OR 1.569; 95% CI 1.328-1.872). After adjusting for all other significant outcome predictors (age, sex, systolic blood pressure, NIHSS score, hypertension, atrial fibrillation, diabetes mellitus, smoking, alcohol abuse, lithic acid, Vit D, HbA1c, glucose), ACA was still an independent prognostic factor, with an adjusted OR of 2.098 (95% CI, 1.762-2.452). In addition, sex, and NIHSS score were independent predictors for stroke outcome (**Table 7**).

Discussion

Our study demonstrated that serum ACA are significantly elevated after a first-ever episode of AIS. Hence, ACA in the serum can be used as a diagnostic biomarker for AIS. In addition, ACA appear to be a key factor in recovery from stroke, since we found that the rate of positive ACA was higher in patients with favorable outcomes. We also confirmed that a positive ACA test was an independent prognostic factor for functional outcomes in AIS cases 3 months after stroke onset. Furthermore, ACA was relat-

Table 7. Univariate and multivariate logistic regression analysis for outcome

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age	1.089	1.012-1.109	0.042	–		
Gender	0.298	0.198-0.327	<0.001	0.065	0.032-0.094	0.021
Systolic blood pressure	0.923	0.846-0.985	0.092	–		
NIHSS score	1.988	1.593-2.439	<0.001	3.123	2.876-3.563	<0.001
Hypertension	0.549	0.346-0.725	0.087	–		
Atrial fibrillation	2.987	1.231-5.342	0.051	–		
Diabetes mellitus	0.703	0.342-1.111	0.092	–		
Smoking	1.222	0.121-4.329	0.023	–		
Alcohol abuse	3.876	1.239-5.382	0.008	–		
WBC (10^9/L)	1.216	0.921-1.345	0.291	–		
Lithic acid (μmol/L)	1.012	0.991-1.043	0.061	–		
Vit D (nmol/L)	1.092	0.932-1.136	0.391	–		
TC (mmol/L)	1.216	0.972-1.482	0.982	–		
TG (mmol/L)	0.982	0.452-1.528	0.438	–		
HDL (mmol/L)	1.098	0.473-2.382	0.176	–		
LDL (mmol/L)	1.452	0.762-2.198	0.451	–		
HbA1c (%)	1.091	0.981-1.201	0.127	–		
Glucose (mmol/L)	1.329	0.872-1.765	0.041	–		
ACA	1.569	1.328-1.872	<0.001	2.098	1.762-2.452	<0.001

OR, Odds ratio; CI, Confidence interval; ACA, anti-cardiolipin antibodies; NIHSS, National Institutes of Health Stroke Scale; WBC, Leukocyte; Vit D, Vitamin D; TC, Total cholesterol; TG, Triglycerides; HDL, High-density lipoproteins; LDL, Low-density lipoproteins; HbA1c, Glycated hemoglobin.

ed to the severity of stroke: the rate of positive ACA increased significantly with a decrease in NIHSS score and infarct volume. Studies have reported that increased production of anti-inflammatory cytokines after stroke was correlated with a lower NIHSS score and a smaller infarct size in animal models and in clinical trials. Thus, we can speculate that ACA may be a protective factor in patients with AIS.

Inflammatory and immune responses play important roles after AIS [19, 20]. In our study, WBC, lithic acid, TC, TG, HDL, and LDL did not differ significantly between patients with favorable and unfavorable outcomes. HbA1c and glucose were associated with functional outcome, but were not predictors for outcomes after AIS. Taken together, the data suggest that serum ACA contributes to the inflammatory response and represents an inflammatory biomarker, as well as being involved in different signaling pathways. The underlying mechanisms remain to be further elucidated.

The inflammatory responses after stroke are known to have a dual function: inflammation may lead to injury after stroke, but may also contribute to recovery processes [21, 22]. A number of studies suggest that anti-inflammatory factors could downregulate the "bad" actions of pro-inflammatory factors [23-25]. Hence, the balance between anti-inflammatory and pro-inflammatory factors is critical in determining the clinical outcome of AIS. The expression of anti-inflammatory agents could reduce ischemic tissue damage.

Our study showed that the patients with increased ACA in the serum had a better clinical outcome at 3 months, suggesting that ACA may be an anti-inflammatory factor and a predictor for the prognosis of AIS. Hence, we speculated that ACA signaling might play an important pathophysiologic and anti-inflammatory role in the process of AIS. Inflammation and the subsequent secondary brain damage are promoted by Th1 cells, while anti-inflammatory responses that reduce secondary brain injury are enhanced by Th2 cells [26]. Many reports suggest that the ACA signaling pathway could tilt the Th1/Th2 balance in favor of Th2 cells [26, 27]. In addition, the increased expression of

important pro-inflammatory cytokines, such as interferon (IFN)-γ and interleukin (IL)-17, contributes to inflammation and ischemic brain damage after stroke [28]. ACA may reduce the production of IFN-γ and IL-17 through inhibiting the actions of Th1 and Th17 cells. The exact mechanisms are still unclear and will need further study. Current knowledge suggests that treatment with anti-inflammatory agents minimizes the infarct size and extends the therapeutic window for ischemic stroke [29]. Therefore, anti-inflammatory therapy may help functional recovery and repair after ischemic brain injury. This suggests that ACA may be a potential target for novel therapeutics aimed at improving the prognosis after AIS.

This study had some limitations. Firstly, we only measured circulating ACA once; therefore, we do not know the dynamic changes in serum ACA at different stages of AIS. Secondly, we tested for plasma ACA, but not cerebral spinal fluid ACA. Thus, whether fluctuations in circulating ACA are the same as those in the CNS is still unknown.

In conclusion, lower rates of positive plasma ACA are related to greater stroke severity and a larger infarction volume among AIS patients. It may be possible to utilize serum ACA as a marker for diagnosis and prognosis among patients who have AIS at admission.

Disclosure of conflict of interest

None.

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